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MINI-REVIEW

Acute disseminated encephalomyelitis: current knowledge and open questions

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Abstract Acute disseminated encephalomyelitis (ADEM) is usually an acute, multi-focal, and monophasic immune-mediated disease of the central nervous system. The disorder is mainly a condition of the pediatric age group, but neurologists are also involved in the management of adult patients. The lack of defined diagnostic criteria for ADEM underlies the limited understanding of its epidemiology, etiology, pathogenesis, course, prognosis, therapy, as well as the association with, and distinction from, multiple sclerosis. The present review summarizes current knowledge and outlines unanswered questions the answers to which should be eventually provided through a synergistic combination of clinical and basic research.

Keywords Acute disseminated encephalomyelitis · Infection · Post infection · Multiple sclerosis · Viruses

Introduction

Acute disseminated encephalomyelitis (ADEM) is an immune-mediated, acute, sometimes subacute or hyperacute, usually transitory, multi-focal, and monophasic inflammatory disease of the central nervous system (CNS) (Tenembaum 2013; Wender 2011). While the condition has diagnostic criteria applicable to the pediatric age group (Krupp and Banwell 2007), there are no defined and accepted criteria for the adult population; as a result, localized abnormalities such as transverse myelitis (Torisu et al. 2010), conditions with recurrences (Cohen et al. 2001), or disorders that affect both the central and the peripheral nervous systems have also been diagnosed as ADEM. This condition affects the pediatric age group more than adults and tends to occur following viral infections, and more rarely vaccinations, the latter scenario being termed post-vaccination encephalomyelitis. In the absence of a biomarker and adult-adjusted criteria, the diagnosis is based on a combination of clinical features, imaging, and cerebrospinal fluid (CSF) findings as well as the exclusion of other infectious and inflammatory neurological and systemic conditions. There are characteristic pathological features that distinguish it from CNS infections as well as multiple sclerosis (MS). This clinical differentiation, however, can be a challenge since brain tissue is seldom available for analysis and the diagnosis is based on both clinical features and neuroimaging, mainly magnetic resonance imaging (MRI).

We suggest that there is inadequate understanding and a lack of consensus in almost all aspects of this condition, from the clinical spectrum and clinical criteria required for diagnosis through to pathogenesis, therapy, and prognosis. The aim of the present review is to summarize current knowledge and to outline key questions which require answers that should be gained by a combination of clinical and basic research.

Epidemiology

In the absence of clear diagnostic criteria, epidemiologic information regarding ADEM should be interpreted with caution. Nevertheless, several facts are evident. Though ADEM can occur at any age, it is usually a disorder of the young,

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including children and young adults. The mean age of clinical presentation in pediatric cohorts ranges from 5 to 8 years (Dale et al. 2000; Hynson et al. 2001; Tenembaum et al. 2002; Anlar et al. 2003). As a previous infection or vaccination is incorporated into the diagnostic criteria, it is not surprising that seasonal disease distributions in the winter and spring months have been reported (Dale et al. 2000; Murthy et al. 2002; Leake et al. 2004). Incidence rates vary and range from 0.64/100,000 (Fukuoka, Japan) (Torisu et al. 2010) to 0.07/100,000 in Germany (Pohl et al. 2007). Most studies suggest a slight male predominance (Tenembaum et al. 2002; Anlar et al. 2003; Murthy et al. 2002).

Where neither previous infection nor vaccination is a criterion for diagnosis, ADEM has been diagnosed in 26 % of certain cohorts without such a preceding event (Tenembaum et al. 2002). Vaccinations include those to both viruses and bacteria (reviewed in 13). Certain pathogens are more liable to lead to ADEM, and the rates quoted are post-measles ADEM in 1:1000, post-varicella ADEM in 1:10,000, and post-rubella ADEM in 1:20,000 (Tselis and Lisak 2005). The association with vaccinations is more prevalent where the latter are produced using neural tissue culture, in particular, the Semple forms of the rabies vaccine and the Japanese B encephalitis vaccine, and when purification was not rigorous enough to exclude the presence of myelin antigen.

The clinical syndrome

Most of the clinical information on the course of ADEM is derived from pediatric cohorts, and there are only a few small-scale studies focusing on the adult population (Schwarz S Mohr A Knauth M Wildemann B Storch-Hagenlocher B Acute disseminated encephalomyelitis: a follow-up study of 40 adult patients. Neurology 2001; Ketelslegers et al. 2011; Sonneville et al. 2009).

No limit or time range for the possible association between infection and disease has been set. Thus, the lag ("incubation") period between infection, viral or bacterial, and ADEM varies from 2 to 30 days or more. Based on limited information, it is possible that while its presentation is similar in the pediatric and adult age groups, the prognosis might be more severe in adults (Sonneville et al. 2009). However, it should be emphasized that the infectious process and the post- infectious, inflammatory condition can overlap (Johnson et al. 1984; Gotkine et al. 2010).

ADEM usually presents with systemic symptoms such as malaise, headache, nausea, vomiting, and fever. These are rapidly followed by focal neurological deficits, reaching a nadir within 4–5 days (Tenembaum et al. 2002). The spectrum of neurological abnormalities is wide and includes depressed consciousness, long tract signs, ataxia, signs of meningeal irritation, spinal cord abnormalities, visual defects, speech impairment, cerebellar disturbances, and seizures (Dale et al. 2000; Hynson et al. 2001; Tenembaum et al. 2002; Anlar et al. 2003; Leake et al. 2004; Mikaeloff et al. 2007). Peripheral nervous system demyelination is not unusual both in the pediatric and the adult age groups. Gray matter involvement (producing behavioral abnormalities, dystonia, and other movement disorders) has also been noted.

Over the years, it has become apparent that the spectrum of severity and clinical disease is quite wide. While children may develop even respiratory failure due to brainstem involvement, subtle disease may well be restricted to nonspecific irritability and headache lasting 1 or 2 days. A benign course ADEM with minimal symptoms or salient clinical findings is not exceptional.

The systemic infection may precede the onset of ADEM, but the symptomatology of infection and pathogen replication in the brain parenchyma can still be present when the immune-mediated pathogenesis takes place (Johnson et al. 1984; Gotkine et al. 2010). It seems, therefore, more appropriate to use the term 'para-infectious' instead of 'post-infectious' in conditions where ADEM clearly follows infection.

The severity of disease may be determined by the nature of the infection, and there have been attempts to correlate the clinical features of ADEM with certain pathogens (Wender 2011).

Acute hemorrhagic leukoencephalomyelitis (AHLE), the most severe form of ADEM, is a hyperacute condition that typically follows influenza or upper respiratory infection and carries a grave prognosis. Demyelination in this variant is widespread with a pronounced neutrophilic infiltrate and necrotic tissue (Leake et al. 2002; Payne et al. 2007). Survival from AHLE depends on early aggressive therapeutic intervention.

Neuroimaging

MRI has become a remarkably sensitive and therefore important tool for the diagnosis of ADEM. The characteristic lesions are best detected on T2-weighted and fluid-attenuated inversion recovery (FLAIR). Magnetization transfer and diffusion tensor MRI may also be helpful in identifying involvement of the so-called normal-appearing white matter.

White matter lesions are typically multiple and asymmetrical (Hynson et al. 2001; Kesselring et al. 1990; Wingerchuk 2003) while gray matter lesions tend to be symmetrical and often involve the thalamus and the basal ganglia (Tenembaum et al. 2002). The lesions are likely to be at the same stage of lesion formation. Rarely, AHLE is manifested by the presence of blood within large T2 hyperintense lesions.

Spinal cord abnormalities on MRI are not infrequent and have been described in 11–28 % of children to include swollen, enhancing intramedullary lesions.

While brain MRI may be helpful, and sometimes mandatory for the differential diagnosis of ADEM, it should be emphasized that the intensity, distribution, and enhancement pattern of lesions do not correlate with prognosis (Tenembaum et al. 2002).

Auxiliary studies

The CSF of ADEM demonstrates mild mononuclear cell increases, a slightly increased protein, and normal glucose with sterile cultures. Oligoclonal IgG bands (OCB) may be present in up to 29 % of patients (Dale et al. 2000; Pohl et al. 2007; Dale and Pillai 2007).

Microbiological investigation to exclude ongoing infection should include pathogen cultures, mainly for bacteria, PCR assays for viruses, including herpes viruses, measles, mumps, etc. and serological assays. The search for the possibility of ongoing infection and subsequent identification of a putative causative pathogen should eventually be determined according to the neurological syndrome, namely white or gray matter abnormality of the CNS and/or spinal cord and PNS involvement.

In AHLE, the CSF pleocytosis is higher and consists also of polymorphonuclears and red cells as well as a higher CSF protein content (Leake et al. 2002; Payne et al. 2007).

Relapsing variants of ADEM: multiphasic or recurrent

ADEM is usually a monophasic condition, with neurological dysfunction that resolves over time. Nevertheless, patients with recurrences have been reported since 1932. The rate of recurrence varies and has even been reported to occur in a third of ADEM patients (Anlar et al. 2003). This rate, however, has not been reported in other studies (Dale et al. 2000; Tenembaum et al. 2002; Mar et al. 2010). The recurrent form of ADEM can take two clinical courses, namely multiphasic, when the clinical presentations represent different brain loci involvement in each relapse or when recurrences have a tendency for the same site to be affected (Cohen et al. 2001). The distinction between multiphasic ADEM and MS is challenging and indeed sometimes not possible (see below).

Recurrent ADEM may reflect either a susceptibility of the physical barriers or antigenic modifications in certain brain regions as a result of an initial local infection and insult. This view is consistent with localized ADEM occurring in the region of an excised brain tumor (Sani et al. 2008) and with recurrent transverse myelitis occurring at the same segmental level (Pandit and Rao 1996).

Diagnosis

Accepted criteria for ADEM diagnosis should be a prerequisite for registering patients into clinical trials and studies aimed at addressing etiologic issues, natural history, course, prognosis, and the effect of therapeutic modalities. No less important, correct diagnosis is mandatory to distinguish ADEM from many entities with a different etiopathogenesis that may require and respond to specific therapies, such as MS, infectious processes, systemic inflammatory conditions, and toxic and metabolic abnormalities. Unfortunately, at present, this most imported tool is not available for adult ADEM.

A panel has proposed definitions for ADEM in childhood, including monophasic and relapsing variants (Krupp and Banwell 2007). It emphasized that ADEM is essentially a diagnosis of exclusion, of a first clinical event with an acute or subacute onset that affects multi-focal areas of the CNS via what appears to be an inflammatory and demyelinating process. The clinical presentation must be multisymptomatic, should include behavioral change, and may also consist of alteration in consciousness. The event has to be followed by clinical and/or radiological improvement. This scheme does not address minor presentations, recurrences, gray matter involvement, or cases that show a single focal abnormality.

The diagnosis of ADEM is also based on neuroimaging which usually shows large multi-focal lesion(s) affecting mainly the white matter with features suggesting that they are of similar age. Nevertheless, exceptions may include diagnosis in cases with a single brain lesion, cases with new or fluctuating signs, MRI findings occurring within 3 months of onset of the initial event, and cases with isolated spinal cord pathology.

The panel also addressed the issue of recurrent ADEM and defined (i) recurrent ADEM, where recurrence involved clinically and radiologically the same brain territory affected during the initial episode and (ii) a multiphasic form, where recurrence involves new brain loci not previously affected, a subgroup that raises the issue of distinguishing between MS and recurrent ADEM.

The distinction between ADEM and MS and neuromyelitis optica

Since they are all acute demyelinating conditions, the clinical distinction between ADEM and an initial acute event(s) of MS or neuromyelitis opica (NMO) is a clinical challenge. All three entities have a different pathogenesis, different therapies, and a different prognosis. Moreover, since many issues regarding etiology, pathogenesis, course, outcome, and therapy of ADEM and MS still eludes us, caution is required in recruiting MS or NMO patients into ADEM studies.

The attempt in 2007 to provide criteria in children below 10 years of age for ADEM and MS (Krupp and Banwell 2007)

highlights this problem. However, the clinical issue has more gray than black and white areas, for example, a child with an initial demyelinating event has a 45 % chance of recurrence (Mikaeloff et al. 2004a), but his/her risk of developing MS by the diagnostic criteria is only 20 % (Mikaeloff et al. 2007). Thus, does a child who has two episodes of CNS demyelination have MS?

The tools to differentiate between ADEM and MS include MRI, CSF OCB, and time. However, there are no criteria to suggest that a child with a single demyelinating episode will eventually develop MS.

Regarding MRI, several studies have examined the risk of an MS course based on the initial MRI scan (Mar et al. 2010; Mikaeloff et al. 2004a, b, 2007; Mikaeloff and Suissa 2004; Callen et al. 2009). A recent MRI study on a relatively large cohort of children suggested that the presence of either one or more T1-weighted hypointense lesions or one or more periventricular lesions was associated with an increased likelihood of MS risk and was highest when both parameters were present (Verhey et al. 2011).

The presence of OCBs in the CSF is also suggestive for MS as in children they are present in 64–95 % of MS patients, but only in 0–29 % of ADEM pediatric patients (Dale et al. 2000; Hynson et al. 2001; Tenembaum et al. 2002; Pohl et al. 2007).

The possibility of NMO may pose another diagnostic challenge. The disorder is characterized by recurrent episodes of transverse myelitis and optic neuritis. The discovery of antibodies against the water channel aquaporin 4 (AQP4) not only suggested the pathogenesis but also provided a biological diagnostic marker of disease (Wingerchuk et al. 2006). However, here again the distinction is far from clear cut. Another antigen, MOG, has been shown to be the target in the disease (Sato et al. 2014), and there are presentations and courses which are now termed neuromyelitis optica spectrum disorders (NMOSD) that have fewer specific clinical and MRI features which extend outside the optic nerves and the spinal cord and are consistent with both MS and ADEM (Sato et al. 2013; Banwell et al. 2008).

Regarding the temporal evolution of lesions, the demonstration of lesion resolution on MRI serial studies supports a diagnosis of ADEM rather than MS, while the appearance of new lesions on follow-up MRI is a powerful predictor of MS development.

Therapy

ADEM treatment is directed primarily toward the acute attacks. Unfortunately, the evidence to support empirical therapy in ADEM is based only on small case series and suffers also from the absence of uniform diagnostic criteria.

Supportive therapy may include intensive care, maintaining fluid and electrolyte balance, controlling seizures, and intubation and ventilation when indicated.

A pathogenesis-oriented therapy is the mainstay of treatment but is not evidence based. Most publications suggest high-dose corticosteroid treatment, usually methylprednisolone given at 20–30 mg/kg/day to a maximum dose of 1 g/day, or dexamethasone given at1 mg/kg/day, followed by oral prednisone taper down for 4–6 weeks (Dale et al. 2000; Hynson et al. 2001; Tenembaum et al. 2002, 2007; Pohl et al. 2007; Gotkine et al. 2010) In children and adults, such therapy requires careful monitoring of serum and urine glucose, blood pressure, and serum potassium.

Immunomodulation has also been reported to be effective in small anecdotal examples. This includes IVIg (total 2 g/kg, over 2–5 days) and plasma exchange, usually five to seven sessions over 7–10 days. Both, however, are not without side effects. The first might be associated with hypercoagulation and the second with anemia, symptomatic hypotension, hypocalcemia, and heparin-associated thrombocytopenia. There is also a risk of catheter-related complications, including thrombosis, septic infections, or pneumothorax.

Prognosis

The long-term prognosis of ADEM is generally favorable, and full recovery is the usual outcome achieved at about 1–6 months post disease. Sequelae may consist of motor difficulties, visual problems, and seizures. Subtle neurocognitive deficits in attention, executive function, and behavior when reevaluated more than 3 years after ADEM have been reported to occur in some cases (Tenembaum et al. 2007; Jacobs et al. 2004).

A quoted fatality rate of 10–15 % probably no longer pertains and does not represent the current state of intensive care and management. The prognosis also depends on the initial type of infection.

Immunopathology

Several pathological features characterize ADEM and are different from those present in MS, suggesting a different pathogenesis (Tenembaum 2013; Sriram and Steiner 2005). These include (1) perivenular T cells and macrophages infiltrates; (2) perivenular demyelination usually around these infiltrates; (3) relative preservation of axons; (4) whereas the white matter takes most of the brunt of disease, the cortex, and deep gray matter structures are not spared; (5) while the pathology is disseminated, the lesions tend be of the same age.

The pathology has some similarity to that of the animal model of experimental autoimmune encephalomyelitis (EAE) (Sriram and Steiner 2005). The latter condition is a monophasic disorder that can be elicited in a spectrum of animals by vaccination with myelin antigens obtained from

myelin proteins. Indeed, ADEM is associated with several instances of vaccination including the Semple rabies vaccine.

This similarity gives credence to the molecular mimicry hypothesis of ADEM which postulates that an infective pathogen stimulates T cell clones that eventually will attack similar or even identical CNS epitopes. Examples of this include myelin peptides that resemble antigens of sequences of human herpes virus (HHV) 6, coronavirus, influenza virus, and Epstein–Barr virus (Sriram and Steiner 2005).

Another possibility is based on the Theiler's murine picornavirus encephalomyelitis virus-induced demyelinating disease (TMEV-IDD) (Johnson et al. 2014). It assumes a direct infection of the brain parenchyma which will expose CNS antigens to the immune system, disrupts the blood–brain barrier, and/or induces secondary infection, exposing CNS-confined antigens to the systemic immune system, thereby abolishing tolerance to autoantigens. In TMEV-IDD, CNS infection with TMEV induces diffuse inflammation and demyelination, followed by a chronic state of T cell reactivity to host CNS myelin peptides resulting in a secondary autoimmune response to myelin components.

Are there specific antigens that serve as targets for the immune reaction in ADEM? There are raised anti-MBP and anti-MOG antibody titers in ADEM patients (O'Connor et al. 2007; Dale and Brilot 2010; Probstel et al. 2011). Studies of cytokines and chemokines in ADEM have shown various upregulated patterns related to activation of macrophages and microglia. CSF analysis has demonstrated a bias toward Th2-type chemokines (CCL17, CCL22) in adult patients with ADEM as are chemokines relevant in the migration of eosinophils and neutrophils, interleukin (IL)-6, and tumor necrosis factor (TNF)-α, as well as the Th2-cytokine IL-10 (Menge et al. 2007; Wingerchuk and Lucchinetti 2007).

A contribution of the immunogenetic background to ADEM pathogenesis has been suggested by the association of certain major histocompatibility complex (MHC) class II alleles with the condition (Tenembaum 2013; Oh et al. 2004).

The recent findings of N-methyl-D-aspartate receptor (NMDAR) antibodies in patients who had herpes simplex virus encephalitis and developed encephalitis (Armangue et al. 2014) or following varicella zoster virus brainstem encephalitis (Schäbitz et al. 2014), compatible with a disease due to anti-NMDAR antibodies that is responsive to immunotherapy (Dalmau et al. 2008) are intriguing. It is another example, almost a metaphor, for the evolving concept of brain infection as a trigger for autoimmune encephalitis.

Conclusions

In the absence of a biological marker, diagnostic criteria are mandatory for a condition where the search for etiology, pathogenesis, prognosis, and therapy is based on clinical cohorts. Such markers will enable patients with a similar disease to be recruited into comparative studies and will also limit and reduce the biological noise of heterogeneity that can mask and confound the ability to identify pathogenesis and assess accurately any therapeutic effects of different treatments.

Unfortunately, diagnostic criteria are lacking for ADEM. Thus, fundamental information is currently unavailable regarding basic aspects of ADEM. This absence results in our inability to answer important questions. Examples of these include the following:

1. Is every post-infectious condition suspected to be immune-mediated, ADEM, or must it follow certain prerequisites such as dissemination (multi-focality) and be time synchronized? It has been suggested by Tselis and Lisak (Tselis and Lisak 2005) that a single lesion is not sufficient for such a diagnosis. But why can a similar pathogenesis not account for a condition confined to a single anatomical locus in the brain or spinal cord, such as retrobulbar optic nerve neuritis, acute transverse myelitis, or acute cerebellar ataxia? Why can transverse myelitis not be an ADEM variant?
2. What are the minimal and maximal allowable lag time periods between infection and a para-infectious neurological condition?
3. When the autoantigen is recognized, such as aquaporin 4 in NMO, or NMDAR post HSE, is this also ADEM? Can a condition confined to gray matter also be ADEM?
4. What is the relationship between ADEM and MS?
5. Has ADEM become a CNS-confined condition? Could CNS disease associated with peripheral radiculo-neuritis also be a variant of ADEM?

These issues have to be addressed and defined in a manner that will pave the way to large multicenter progressive studies that will enable us to elucidate the etiopathogenesis of ADEM and provide rational, evidence-based therapy for this enigmatic condition.

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